

# Accelerated Partial Breast Irradiation as Sole Radiotherapy After Breast-Conserving Surgery for Early Stage Breast Cancer



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## Executive Summary

### Background

Survival after breast-conserving therapy (BCT) is equivalent to survival after mastectomy for patients diagnosed with tumors categorized as stage I or II. BCT is a multi-modality treatment that consists of breast-conserving surgery to excise the tumor with adequate margins, followed by whole-breast external-beam radiation therapy (WB-EBRT) administered as 5 daily fractions per week over 5 to 6 weeks. Local boost irradiation to the tumor bed often is added to whole-breast irradiation to provide a higher dose of radiation at the site where recurrence most frequently occurs. For some patients, BCT also includes axillary lymph node dissection or irradiation of the axilla. Brachytherapy for breast cancer is the implantation of radioactive material directly in the breast tissue.

Accelerated partial-breast irradiation (APBI) differs from WB-EBRT in two ways. First, the radiation targets only a segment surrounding the tumor rather than the entire breast. Second, since the duration of treatment is 4 to 5 days rather than 5 to 6 weeks, radiation is delivered in fewer fractions at larger doses per fraction. There are several methods of delivering APBI, including interstitial or balloon brachytherapy, intensity-modulated radiotherapy (IMRT), 3-dimensional conformal radiotherapy (3D-CRT), and intraoperative radiotherapy. A prior Assessment (Vol. 17, No. 18; 2002) concluded that APBI using brachytherapy did not meet the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria, because there was insufficient evidence to determine whether it was as beneficial as WB-EBRT following BCT. The current Assessment updates the 2002 Assessment.

Note that treatment of early stage breast cancer by brachytherapy without surgical excision has not been studied adequately and is not addressed in this Assessment.

### Objective

To evaluate whether evidence shows that for women with tumors smaller than 2–3 cm, clean margins, and no more than 3 positive nodes, APBI as sole radiation post breast-conserving surgery improves net health outcomes at least as much as WB-EBRT.

### Search Strategy

A literature search was conducted on MEDLINE® from 2004 through December 2006, using the following search terms: the Medical Subject Headings (MeSH®) terms “breast neoplasms” and “brachytherapy,” plus text word searching for “breast” and [“brachytherapy” or “radiation” or “radiotherapy”]. Reference lists were also reviewed. The search yielded 87 references, which were searched for studies on the impact of accelerated partial breast irradiation on recurrence rates and mortality. The search was updated in May 2007, using the search terms “accelerated partial breast irradiation” or

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“APBI,” “breast neoplasm,” “radiotherapy,” and “brachytherapy.” At that time, 199 citations were reviewed.

### **Selection Criteria**

All English-language articles in peer-reviewed journals on APBI that reported on breast cancer recurrence with at least 25 subjects were included if they reported on a control group (n=6). Uncontrolled studies with a mean or median follow-up of at least 5 years were also included (n=2). Abstracts were excluded.

### **Main Results**

There is only one randomized trial comparing APBI using interstitial brachytherapy and the established alternative, WB-EBRT, for patients with early stage breast cancer undergoing breast-conserving surgery. The recurrence rates for APBI and WB-EBRT were similar. However, the trial was small (n=126); and the preliminary report covered only 30 months of follow-up, far short of the 8 years needed to assess the impact of radiotherapy on breast cancer recurrence and on mortality. It also included two types of APBI, because 17 patients were unsuitable for interstitial brachytherapy, and one cannot determine whether the impact is the same for each kind of brachytherapy.

Five nonrandomized, controlled studies (n=1,001) compared interstitial brachytherapy with whole-breast irradiation. No significant differences in recurrence rates were found between the two types of radiotherapy. However, these studies have a number of limitations, including relatively small sample sizes, short follow-up (one study), and most importantly, potential baseline differences between the intervention and control arms. Two noncontrolled studies examined interstitial brachytherapy (n=84) and had a median follow-up of 57 and 91 months. The ipsilateral failure rate was 4% in the study with shorter follow-up and 15% in the other study, which had 15% node-positive subjects.

Of the many studies on balloon brachytherapy, none met the Assessment study selection criteria: All were uncontrolled, and all either had insufficient follow-up or failed to report on recurrence and/or mortality rates. No studies were found that addressed outcomes from APBI using 3D-CRT or IMRT. Two studies examined intraoperative APBI; however, they either did not have long enough follow-up or they did not report on recurrences.

### **Author’s Conclusions and Comments**

The critical question is whether APBI is as effective as WB-EBRT in reducing recurrences and mortality in patients undergoing BCT. To assess APBI as a sole alternative to WB-EBRT, trials are needed that compare the two approaches in similar populations (ideally randomized) for at least 8 years. In a patient-level meta-analysis, the Early Breast Cancer Trialists’ Collaborative Group found that the use of WB-EBRT reduced 15-year breast cancer absolute mortality risk by 5.4%, from 35.9% to 30.5% (SE=1.7, 2p=0.0002); there was a similar reduction in absolute mortality from all causes of 5.3% (SE=1.8, 2p=0.005). Thus, evidence clearly demonstrates that radiotherapy following BCS reduces recurrences and prolongs survival.

There are 32 studies on APBI, but only 6 are controlled studies; and the rest are uncontrolled. There is only one small, randomized trial (n=126) with inadequate follow-up (30 months). It is uncertain whether controls in the nonrandomized studies are sufficiently similar to the intervention groups. Recurrence rates vary substantially based on multiple clinical factors, not all of which have been identified; thus, one cannot be sure that 5-year recurrence rates in nonrandomized trials are equivalent between WB-EBRT treatment and APBI. Given the various APBI techniques, there may also be differences in dosimetry, delivery, and adverse effects, and outcomes among the modalities.

There are a number of randomized, controlled trials on the use of APBI currently underway, comparing whole-breast irradiation to 1) intraoperative electron beam radiation therapy (European Institute of Oncology, n=824); 2) interstitial or balloon brachytherapy or 3D-CRT (NSABP B 39/RTOG 0415, n=3,000); 3) interstitial brachytherapy (European Brachytherapy Breast

Cancer GEC-ESTRO, n=1,170); 4) interstitial brachytherapy or electrons (National Institute of Oncology, Hungary, n=570); and 5) 3D-CRT (Ontario Clinical Oncology Group, n=2,128) (www.clinicaltrials.gov and Marsiglia and Chajon 2006).

Some proponents of APBI have pointed to the number of women who forego radiotherapy following BCS. They assert that APBI is more convenient than WB-EBRT, and therefore, its availability might reduce the number of patients with no radiotherapy. Radiotherapy use is less frequent among African-Americans and those living farther from radiotherapy facilities; however, adequate information is lacking on other factors influencing women who do not get radiotherapy. Therefore, it is not known whether patients currently omitting radiotherapy would choose APBI if it were readily available. Also, some women may choose to forego radiotherapy because of older age, as suggested in the National Comprehensive Cancer Care Network (NCCN) guidelines, or the presence of other life-threatening comorbidities.

Furthermore, if convenience is the primary impediment to getting radiotherapy following BCS, several accelerated whole-breast protocols have been tested. For example, a randomized controlled trial in Canada compared the traditional 50-Gy protocol delivered in 25 fractions over 35 days with an accelerated protocol of 42.5 Gy delivered in 16 fractions over 22 days. With 1,234 patients followed a median of 69 months, there was no statistically significant difference in local recurrence-free, disease-free, or overall survival between the two regimens. Another study comparing 3 whole-breast fractionation regimens suggested that hypofractionation is a reasonable alternative; a larger trial is underway to confirm these findings. Other accelerated, whole-breast regimens are currently being tested, but the studies reported to date are uncontrolled and the follow-up is too short to evaluate the impact on recurrence rates. Because accelerated whole-breast irradiation changes only one parameter in the traditional radiotherapy regimen, i.e., fraction size but not the breast volume treated, it may be a more conservative approach than APBI for women who do not want to undergo the traditional 5- to 6-week protocol. This may be a more prudent approach until further follow-up reveals the long-term effectiveness of APBI versus the conventional WB-EBRT protocol.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether accelerated partial-breast irradiation (APBI) as sole radiotherapy meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria to decrease recurrence after breast-conserving surgery for early stage breast cancer.

**1. The technology must have final approval from the appropriate governmental regulatory bodies.**

Iodine-125 seeds were marketed prior to enactment of the 1976 Medical Device Amendments. Thus, they were cleared for marketing on a “grandfathered” basis. Subsequent radioactive isotope implants, including iridium-192, were approved via 510(k) as substantially equivalent to the radioactive iodine seeds.

A number of breast brachytherapy devices have received U.S. Food and Drug Administration’s (FDA) 510(k) marketing clearance. The MammoSite™ RTS was cleared for marketing via 510(k) in May 2002 as substantially equivalent to other commercially available brachytherapy applicators used with sealed radiation sources. The FDA’s Office of Device Evaluation judged it reasonably likely that the device will be used in ways outside those specified in the proposed labeling, and that such use could cause harm. Therefore, the FDA required inclusion of the following statement in the “Warnings” section of the device’s labeling: “The safety and effectiveness of the MammoSite RTS as a replacement for whole breast irradiation in the treatment of breast cancer has not been established.”

In December 2005, the FDA cleared for marketing the Axxent™ Electronic Radiotherapy device (Xoft, Inc., Fremont, CA) via 510(k) as substantially equivalent to the MammoSite™ and other

brachytherapy systems. The Axxent™ device is a balloon brachytherapy system that uses a disposable, microminiature radiation source to deliver the radiation rather than radioisotopes.

Three additional devices used for breast brachytherapy recently received 501(k) clearance from the FDA. First is a remote-controlled radionuclide applicator system by BioLucent, Inc. (Aliso Viejo, CA), called the Strut-Adjusted Volume Implant or SAVI™, which was cleared on October 20, 2006. This device is described by the manufacturer as a hybrid approach, combining interstitial brachytherapy and balloon brachytherapy. Like balloon brachytherapy, the device is inserted in the tumor cavity through a small incision. A bundle of catheters is then spread out to form an ellipsoid shape inside the cavity. Second is the Adjustable Multi-Catheter Source Applicator or ClearPath™ from North American Scientific, Inc. (Chatsworth, CA), which was cleared on November 9, 2006. The third is the SenoRad Multi-Lumen Balloon Source Applicator for Brachytherapy from SenoRx, Inc. (Aliso Viejo, CA), which was cleared on May 18, 2007.

## **2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.**

The Assessment sought to compare outcomes of APBI, with those of WB-EBRT, after breast-conserving surgery. Follow-up of at least 8 years is needed to demonstrate their equivalence.

The single randomized, controlled trial reported follow-up of only 30 months, far short of the minimum needed. Other studies reported on longer follow-up but were uncontrolled, did not report on recurrences, included patients who did not meet the eligibility criteria, or had other important flaws. All of the studies that met the study selection criteria for this Assessment focused on interstitial brachytherapy, a technique with a steep learning curve for practitioners. These findings cannot be extrapolated automatically to other types of APBI.

Consequently, the evidence on APBI as sole radiotherapy for early stage breast cancer is insufficient to permit conclusions concerning its effect on health outcomes.

## **3. The technology must improve the net health outcome.**

Since available evidence is insufficient to permit conclusions, it cannot be determined whether APBI as sole radiotherapy improves net health outcomes of women undergoing breast-conserving surgery for early stage breast cancer.

## **4. The technology must be as beneficial as any established alternatives.**

Since available evidence is insufficient to permit conclusions, it cannot be determined whether APBI as sole radiotherapy is as beneficial as WB-EBRT after breast-conserving surgery for early stage breast cancer.

## **5. The improvement must be attainable outside the investigational settings.**

Whether APBI using as sole radiotherapy improves health outcomes after breast-conserving surgery for early stage breast cancer has not been demonstrated in the investigational setting.

Based on the above, accelerated partial breast irradiation as the sole radiation treatment after breast-conserving surgery for early stage breast cancer does not meet the TEC criteria.

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## Assessment Objective

Survival after breast-conserving therapy (BCT) is equivalent to survival after mastectomy for patients diagnosed with tumors categorized as stage I or II. BCT is a multi-modality treatment that consists of breast-conserving surgery to excise the tumor with adequate margins, followed by whole-breast external-beam radiation therapy (WB-EBRT) administered as 5 daily fractions per week over 5 to 6 weeks. Local boost irradiation to the tumor bed often is added to whole-breast irradiation to provide a higher dose of radiation at the site where recurrence most frequently occurs. For some patients, BCT also includes axillary lymph node dissection or irradiation of the axilla. A number of randomized, controlled trials have demonstrated that the addition of radiotherapy after breast-conserving surgery reduces recurrences and mortality (EBCTCG 2005).

Accelerated partial-breast irradiation (APBI) has been proposed as an alternative to WB-EBRT. It differs from WB-EBRT in several ways. First, the radiation targets only a segment surrounding the area where the tumor was removed rather than the entire breast. Second, the duration of treatment is 4 to 5 days rather than 5 to 6 weeks, so the radiation is delivered in fewer fractions at larger doses per fraction. Third, the radiation dose is intrinsically less uniform within the target volume when APBI uses brachytherapy, which refers to the implantation of radioactive material directly in the breast tissue, since it declines as the inverse square of distance from the small sources implanted internally. In contrast, the parallel-opposed tangential fields used for WB-EBRT provide relatively homogeneous doses in the breast.

There are several methods of delivering APBI, including interstitial and balloon brachytherapy, intraoperative radiation therapy, 3-dimensional conformal radiation therapy (3D-CRT), and intensity-modulated radiation therapy (IMRT). A prior Assessment (Vol. 17, No. 18; December 2002) examined the use of brachytherapy as sole radiotherapy following breast-conserving surgery in early stage breast cancer. It concluded that APBI using brachytherapy as the sole radiation treatment after breast-conserving surgery for early stage breast cancer did not meet TEC criteria, because there was insufficient evidence regarding the impact of APBI on recurrence and mortality.

Of particular concern was the lack of long-term follow-up and the fact that the only randomized, controlled trial was relatively small (n=63 per arm) and had only 30 months of follow-up.

When compared with whole-breast irradiation, APBI using brachytherapy or other techniques offers potential advantages of convenience and decreased radiation dose to healthy breast tissue. However, data on outcomes are needed to resolve several concerns. Radiobiologic principles based on laboratory studies suggest accelerated dosing with fewer fractions may decrease effectiveness. So the first key question is whether APBI is as effective as WB-EBRT for preventing recurrences near the tumor site. Second, one of the reasons BCT is as effective as mastectomy is presumably because the WB-EBRT treats any small lesions in other parts of the breast that are not visible on mammography. The question then becomes whether there is a subset of patients in whom the risk of ipsilateral tumors away from the tumor site is low enough that APBI is sufficient. Because the natural history of the disease indicates that recurrence elsewhere in the breast may occur more than 5 years after treatment, longer-term follow up of patients given WB-EBRT versus APBI is needed to answer the second question: Are patients undergoing APBI more likely to have distant recurrence in the ipsilateral breast? If the answer is no, it could be because either 1) this group of patients is very unlikely to develop lesions elsewhere in the breast, and/or 2) WB-EBRT may not be effective in treating more distant, ipsilateral lesions.

This Assessment reviews the available evidence to compare the outcomes of APBI with those of WB-EBRT after breast-conserving surgery among women with tumors smaller than 2–3 cm, clean margins, and no more than 3 positive nodes. Since brachytherapy only irradiates part of the breast, the Assessment seeks evidence on ipsilateral breast tumor recurrences (IBTR) and also compares these alternatives with respect to cosmesis and adverse effects. IBTR is the main outcome used in studies that compare methods of breast-conserving therapy, as survival is also affected by the effectiveness of therapy for any recurrences.

Note that treatment of early stage breast cancer by brachytherapy without surgical excision has not been studied adequately and is not addressed in this Assessment.

## Background

### Breast Conserving Therapy

Early invasive breast carcinoma includes tumors 5 cm or smaller in largest dimension, with dissemination limited to moveable ipsilateral axillary lymph nodes (Physician Data Query 2002; Winer et al. 2001). The American Joint Committee on Cancer/International Union against Cancer staging system groups these patients (T1-2, N0-1, M0) in stages I, IIA, or IIB (excluding those with T3 tumors). Patients with advanced breast cancer have tumors larger than 5 cm or have disease spread to ipsilateral axillary lymph nodes that are fixed to each other or other structures, ipsilateral internal mammary lymph nodes, or distant sites.

Evidence from randomized, controlled trials and retrospective studies with 10–20 years of follow-up have shown that long-term survival after BCT is equivalent to survival after mastectomy, while avoiding the disfigurement of more radical surgery (for reviews, see Physician Data Query 2002; Morrow et al. 2002; Winer et al. 2001; Early Breast Cancer Trialists' Collaborative Group 1995, 2005; Abrams et al. 1995; NIH Consensus Development Conference 1991). In the randomized trials, BCT included breast-conserving surgery to excise the tumor with adequate margins, plus postoperative external-beam radiation therapy targeting the whole breast (WB-EBRT).

Most patients diagnosed with stage I or II breast cancer now are offered a choice of BCT or modified radical mastectomy, but BCT is selected less often than expected. The inconvenience of radiation therapy may be a factor in acceptance of BCT. Studies have shown that those living furthest from treatment facilities are least likely to select BCT instead of mastectomy and to undergo radiation therapy after breast-conserving surgery (Farrow et al. 1992; Athas et al. 2000; Nattinger et al. 2001). The inconvenience of 5 to 6 weeks of daily radiation treatments may be a factor even when facilities are nearby (Vicini et al. 2001, 2002). Thus, there has been interest in the hypotheses that breast-conserving surgery without WB-EBRT or with faster and more limited radiation techniques, might be adequate for women at lowest risk of ipsilateral breast tumor recurrence (IBTR).

No current data were found on the percentage of BCT patients not having radiation therapy; more recent articles report patterns in those

undergoing BCT in the late 1990s or early 2000s (Voti et al. 2006). A study of women diagnosed in Florida between July 1997 and December 2000 found that 19% of those having lumpectomy did not receive radiation therapy (Voti et al. 2005). A study using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) tumor registries from 1992 to 2002 examined how many women with early stage (I or II) breast cancer received radiotherapy within 4 months following breast-conserving surgery (Du et al. 2007). After adjusting for age, they found that in 2002, 30.8% of Caucasian women and 44.7% of African-American women had not received radiotherapy. Furthermore, these rates had increased since 1992 from 24.7% for Caucasians and 34.0% for African-Americans. Although these numbers could be somewhat inflated by underreporting of radiotherapy, a study comparing radiation therapy use from 1991 to 1996 among patients 65 or older using SEER and Medicare claims data found 94.2% agreement ( $\kappa=0.87$ ) between the 2 data sources when looking at all breast cancers (Virnig et al. 2002).

In contrast to quality of life after mastectomy versus BCT (reviewed by Kiebert et al. 1991), data are lacking to compare quality of life after breast-conserving surgery with versus without WB-EBRT. Survey data also are lacking to compare the importance of factors that underlie decisions to decline WB-EBRT after breast-conserving surgery. In a study interviewing the surgeons of 119 women who did not receive guideline-recommended adjuvant therapy at 6 hospitals in New York City in 1999–2000, surgeons did not recommend the therapy for 35% of these women; 31% of the patients declined therapy; and the surgeon could not identify the reason for underuse for 34% of the women, which the authors classified as system failures (Bickell et al. 2007). However, the study did not report separately on the 39% of these women who did not receive radiotherapy, nor did it indicate the reasons for patients' refusal.

### Effect of WB-EBRT as a Component of Breast-Conserving Therapy

Multiple randomized trials reported that postoperative WB-EBRT significantly reduced IBTRs after breast-conserving surgery (for reviews see Abrams et al. 1995; Early Breast Cancer Trialists' Collaborative Group 2000; Wazer 2000; Small 2001; Winer et al. 2001; Physician Data Query 2002). In some, multivariate analyses

found no patient subgroup with sufficiently low risk of IBTR to avoid using WB-EBRT in BCT (Fisher et al. 1995; Veronesi et al. 1995a; Clark et al. 1996; Liljegren et al. 1999). Consequently, clinical guidelines strongly recommend post-operative WB-EBRT for those undergoing breast-conserving surgery (Morrow et al. 2002; Winchester and Cox 1998; Goldhirsch et al. 1998), and a NIH Consensus Statement defined the standard of care for BCT as breast-conserving surgery followed by WB-EBRT (NIH Consensus Development Conference 2000). Most recently, National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-21 showed that WB-EBRT significantly reduced the actuarial estimate for incidence of IBTR at 8 years (from 16.5% to 2.8%;  $p < 0.0001$ ), even for patients receiving tamoxifen whose tumors were 1 cm or less in largest dimension, were excised with tumor-free margins, and had not spread to axillary lymph nodes (Fisher et al. 2002a).

Multiple studies showed that overall prognosis is poor when cancer recurs locally after BCT or modified radical mastectomy, with relative risk for mortality increased by a factor of 3.4 to 8.8 (Fisher et al. 1991; Whelan et al. 1994; Kemperman et al. 1995; Veronesi et al. 1995b; Fortin et al. 1999). Patients infrequently select repeat BCT to treat IBTR, either because they no longer are suitable candidates or because they believe more radical surgery will minimize subsequent recurrences. Thus, recurrent tumor after BCT usually results in more extensive and disfiguring surgery (mastectomy), and exposes patients again to risks of morbidity and mortality from anesthesia and surgery.

While initial results did not find any effect of WB-EBRT on survival, longer follow-up has revealed that it also increases survival. In a patient-level meta-analysis, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG 2005) found that WB-EBRT reduced the 15-year breast cancer absolute mortality risk by 5.4%, from 35.9% to 30.5% (SE=1.7,  $2p = 0.0002$ ); while absolute mortality from all causes similarly decreased by 5.3% (SE=1.8,  $2p = 0.005$ ).

There are differences of opinion among healthcare professionals. The National Comprehensive Cancer Care Network (NCCN 2007) recommends radiation therapy to the whole breast with boost for patients with clinical stages I, II, and T2N1M0 breast cancer undergoing lumpectomy (additional chemo-

therapy is also discussed). In a footnote, they amplify as follows: "Whole breast irradiation with boost (by photons, brachytherapy or electron beam) to tumor bed. Boost to tumor bed is especially encouraged in those 50 y of age or younger. Partial breast irradiation should be performed only as part of a high-quality prospective clinical trial."

The NCCN guidelines also state in a footnote: "Breast irradiation may be omitted in those 70 y of age or older with estrogen-receptor positive, clinically node negative, T1 tumors who receive adjuvant hormonal therapy (category 1)." An article on use of lumpectomy and tamoxifen with or without whole-breast radiotherapy in this same population found that the addition of radiation had no impact on rates of mastectomy for local recurrence, distant metastases, or 5-year rates of overall survival (Hughes et al. 2004). However, the rate of local or regional recurrence at 5 years was 1% in the group receiving tamoxifen and radiation and 4% in the group taking tamoxifen alone ( $p < 0.001$ ). The authors conclude that "Lumpectomy plus adjuvant therapy with tamoxifen alone is a realistic choice for the treatment of women 70 years of age or older who have early, estrogen-receptor-positive breast cancer." It should be noted, however, that 5 years may not be long enough to detect any differences in overall survival. This position also raises the possibility that some of the patients undergoing BCS without radiation may have chosen not to have radiation in accordance with the above recommendations.

In contrast, the American Society of Breast Surgeons (ASBS 2005) recommends the following selection criteria when considering patients for treatment with APBI as a sole form of radiation therapy: patient is 45 years or older, has invasive ductal carcinoma or ductal carcinoma in situ (DCIS), has a tumor 3 cm or smaller, has negative microscopic surgical margins of excision, and has negative axillary lymph nodes or sentinel lymph node.

#### **Accelerated Partial Breast Irradiation**

Although there are differing views on the appropriateness of APBI as sole radiotherapy for early stage breast cancer, it is generally agreed that APBI is appropriate, if at all, for only a select group of patients with a low risk of recurrence. Although the precise criteria vary from study to study, in general, the focus is on older patients with smaller tumors whose

disease is node negative (or limited to 1 to 3 positive nodes) with no sign of malignancy in the surgical margins; lobular carcinoma is usually excluded.

APBI differs from WB-EBRT by targeting a smaller portion of the breast and delivering the radiation in fewer, larger doses (although the cumulative dose is smaller). With brachytherapy, the radiation dose is intrinsically less uniform within the target volume. Investigators hypothesize these differences may offer potential advantages to APBI compared with WB-EBRT (Kuske 1999; Nag et al. 2001; Vicini et al. 2002). These include increased convenience and fewer logistical problems, due to shorter treatment times; and less radiation to normal breast and surrounding tissues, since treatment targets are more narrowly focused. On the other hand, potential disadvantages of APBI compared with WB-EBRT may include increased risk for recurrence elsewhere in the breast, since radiation is limited to a segment surrounding the tumor site; and a narrower therapeutic index (the ratio between therapeutically effective and toxic doses), since it uses few fractions with larger doses per fraction.

Potential disadvantages of brachytherapy for APBI vary with the method used. Interstitial brachytherapy is more invasive, since interstitial catheters are implanted; it also has limited availability, since special expertise is required. Balloon brachytherapy may cause dose inhomogeneity because it uses a small, spherical source, and thus may underdose portions of the target volume. Balloon brachytherapy also is not always successful, and around 10–20% of implanted devices have to be explanted. In some cases, this is because the device is implanted during the breast-conserving surgery, and subsequent pathology results reveal that the device is not indicated since margins or skin spacing are inadequate or the lumpectomy cavity is shaped irregularly. Additionally, use of any method for APBI is inadvisable with certain histologies such as lobular carcinoma or the presence of an extensive intraductal component.

Another important question for this Assessment is the duration of follow-up needed to determine whether local control after breast-conserving surgery plus APBI using brachytherapy is equivalent to that after breast-conserving surgery plus WB-EBRT. The time course of IBTRs after breast-conserving surgery

can help answer this question (see Table 1). Five trials randomized patients to breast-conserving surgery with radiotherapy versus without radiotherapy and reported data that permit comparison of estimated frequencies for IBTRs at 5 years after treatment (Fisher et al. 2002a; Liljegren et al. 1994, 1999; Mariani et al. 1998; Clark et al. 1996; Fisher et al. 1995, 2002b). Additional data on IBTRs up to and after 5 years were reported by a pooled analysis of 3 randomized trials that compared differing extents of surgery in breast-conserving surgery with or without radiotherapy (Veronesi et al. 1995a), 2 nonrandomized studies with historical controls (Hermann et al. 1993; Clark et al. 1987), 4 uncontrolled, single-arm series of patients treated by breast-conserving surgery plus WB-EBRT (Resch et al. 2002; Frazier et al. 2001, Vicini et al. 1997a; Boyages et al. 1992; Recht et al. 1988). The Early Breast Cancer Trialists' Collaborative Group's (2005) patient-level meta-analysis examined isolated local recurrence with versus without post-lumpectomy radiation over a 15-year period for node-negative and node-positive disease separately.

Two of the randomized trials limited enrollment to patients with tumors of 1 cm or less (Fisher et al. 2002a) or of 2 cm or less (Liljegren et al. 1994, 1999) in largest dimension, with margins verified free of tumor by a pathologist using microscopy, and with lymph nodes demonstrated free of tumor after axillary dissection. Except for a minority with lobular histology or an extensive intraductal component, patients in these randomized trials would meet selection criteria of recent controlled studies on APBI. Most clinicians agree patients in the NSABP B-21 and Liljegren trials have the smallest risk for IBTR after BCT. Nevertheless, 10% to 18% recurred by 5 years after breast-conserving surgery without radiotherapy, and 5% to 6% more recurred after 5 years in each trial. Significantly fewer IBTRs occurred among patients randomized to breast-conserving surgery plus WB-EBRT: 2% to 4% by 5 years and 1% to 6%, thereafter.

Those with smallest tumors (1 cm or less; Fisher et al. 2002a) given tamoxifen and WB-EBRT after breast-conserving surgery had the lowest frequency of IBTRs (2% by 5 years and only 0.8% more, for a total of 2.8% by 8 years). Note also that, except for this arm of the NSABP B-21 trial, Kaplan-Meier curves for cumulative incidence of IBTR (Fisher et al. 2002a) or for freedom from local recurrence

**Table 1.** Ipsilateral Breast Tumor Relapses (IBTR) 5 Years and Later After Breast-Conserving Surgery ± Radiotherapy

Citation, Study Design & Accrual Period	Eligibility Criteria	Treatment Arm	Median Follow-up	n	IBTR Rate at 5 Years (%)	Last Estimate for IBTR Rate	Final IBTR Rate (%)	IBTRs After 5 Years (%)
Fisher et al. 2002a (NSABP B-21) randomized trial 6/89 to 12/98	invasive breast tumor ≤1 cm in largest dimension; lumpectomy with tumor-free margins by pathology; axillary dissection with negative lymph nodes	surgery + tam + WB-EBRT	87 mos.	334	2	8 years	2.8	0.8
		surgery + placebo + WB-EBRT	86 mos.	332	4		9.3	5.3
		surgery + tam	89 mos.	334	10.5		16.5	6.5
Liljegren et al. 1994, 1999 randomized trial 1981 to 1988	unifocal tumor ≤2 cm diameter on mammogram; sector excision with tumor-free margins ≥2 cm; axillary dissection with negative lymph nodes	surgery + WB-EBRT	109 mos.	184	2.3	10 years	8.5	6.2
		surgery alone	103 mos.	197	18.4		24.0	5.6
Mariani et al. 1998 randomized trial 1985 to 1987	unilateral breast cancer ≤2.5 cm diameter; adjuvant systemic therapy if positive nodes	quadrantectomy + 50 Gy WB-EBRT + 10 Gy boost	113 mos.	360	4.7	10 years	7.4	2.7
		lumpectomy + 45 Gy WB-EBRT + 16 Gy boost		345	11.6		18.6	7.0
			237 margin- 46 margin+	10.6	17.6		7.0	
Clark et al. 1996 randomized trial 4/84 to 2/89	invasive breast tumor ≤4 cm in largest dimension; excised with 0.5–1 cm tumor-free margins by pathology; axillary dissection with negative lymph nodes	surgery + WB-EBRT + boost	91 mos.	416	10	10 years	15	5
		surgery alone			(as first event)		(as first event)	(as first event)
			421	32	40		8	
Fisher et al. 1995, 2002b; (NSABP B-06) randomized trial 4/76 to 1/84	invasive breast tumor ≤4 cm in largest dimension; excised with tumor-free margins by pathology; axillary dissection with negative or positive lymph nodes	surgery + WB-EBRT	144 mos.	567	5	20 years	14	9
				375 node- 192 node+	4		17	13
		surgery alone		2	9		7	
			570	27	39		12	
			361 node- 209 node+	25	36		11	
		35	44	9				

**Table 1.** Ipsilateral Breast Tumor Relapses (IBTR) 5 Years and Later After Breast-Conserving Surgery ± Radiotherapy (cont'd)

Citation, Study Design & Accrual Period	Eligibility Criteria	Treatment Arm	Median Follow-up	n	IBTR Rate at 5 Years (%)	Last Estimate for IBTR Rate	Final IBTR Rate (%)	IBTRs After 5 Years (%)
Veronesi et al. 1995a follow-up pooled analysis of 3 RCTs, 1973 to 1989	invasive breast cancer ≤2.5 cm diameter, node negative after axillary dissection	quadrantectomy + WB-EBRT	82 mos. (192, 79,	708	2.5	10 years	6.5	t4
		lumpectomy + WB-EBRT	52 mos. for trials 1 to 3)	225	14	8 years	23	9
Hermann et al. 1993 retrospective, nonrandomized 1975 to 1988	partial mastectomy for stages 0 to II; selected for radiation if positive nodes, lymphatic invasion, nuclear atypia, or close margins	surgery plus WB-EBRT	102 mos. (mean)	289	5	10 years	14	9
		surgery alone		620	11		16	5
Clark et al. 1987 retrospective nonrandomized 1958 to 1984	49% T1, 27% T2; clinically node- negative with (early years) or without axillary dissection	surgery + WB-EBRT	NR	1,108	10	10 years	14	4
		surgery alone		396	24		29	5
Resch et al. 2002 retrospective series; 1982-92	66% T1, 31% T2; 62% node negative; extent of surgery varied	surgery + WB-EBRT + boost	104 mos. (mean)	410	2	10 years	4	2
Frazier et al. 2001; Vicini et al. 1997a retrospective series; 1980-1989	72% T1, 28% T2; 71% N0, 23% N1, 5% Nx; 100% M0; 59% stage I, 41% stage II	surgery + WB-EBRT + boost	116 mos.	552	3	13 years	11	8
Boyages et al. 1992 retrospective series; 1979-85	69% T1, 31% T2; 97% N0 or N1A; 66% stage I, 34% stage I; extent of surgery varied; 62% had axillary dissection	surgery + WB-EBRT (+ boost for all but 12)	73 mos.	131	4	10 years	13	9

**Table 1.** Ipsilateral Breast Tumor Relapses (IBTR) 5 Years and Later After Breast-Conserving Surgery ± Radiotherapy (cont'd)

Citation, Study Design & Accrual Period	Eligibility Criteria	Treatment Arm	Median Follow-up	n	IBTR Rate at 5 Years (%)	Last Estimate for IBTR Rate	Final IBTR Rate (%)	IBTRs After 5 Years (%)
Recht et al. 1988 retrospective series; 1968 to 1981	stage I or II invasive cancer given BCT; 54% T1, 46% T2; 48% node negative, 24% node positive, 27% nodes uncertain	resection + WB-EBRT + boost	75 mos.	607	10 8% TR/MM 1% elsewhere in same breast	10 years	16 11% TR/ MM 4% elsewhere in same breast	6 3% TR/ MM 3% elsewhere in same breast
Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2005	subanalysis of node-negative patients in 10 randomized trials	BCS + radiation therapy  BCS alone	NR	6,097	6.7  22.9	numerical value reported for 10 years; graph goes to 15 years	10.0  19.2	3.3  3.7
Individual-level meta-analysis through 2000 for studies starting by 1995								
<b>Abbreviations</b>								
BCT	breast conserving therapy							
mos.	months							
tam	tamoxifen							
TR/MM	true relapse or marginal miss							
WB-EBRT	whole-breast external-beam radiation therapy							

(Liljegren et al. 1999) apparently did not reach plateaus until 8 years or later. These data argue strongly that one needs at least 7 to 8 years of follow-up to compare IBTR frequencies after breast-conserving surgery plus APBI using brachytherapy with those after breast-conserving surgery plus WB-EBRT, even for those at lowest risk of ipsilateral recurrence.

Only one study in Table 1 (Recht et al. 1988) reported frequencies separately for IBTRs classified as true relapses or marginal misses (TR/MM), and those that occurred elsewhere in the same breast that permit comparison for recurrences up to 5 years with those after 5 years. While “elsewhere” recurrences were relatively infrequent (total of 4%), three-fourths of these occurred after 5 years. Other studies reported cumulative rates of TR/MM and elsewhere IBTR, but without comparing early versus late recurrences (Mariani et al. 1998; Clark et al. 1987; Resch et al. 2002; Frazier et al. 2001; Boyages et al. 1992). Cumulative rates of IBTR outside the surgical site ranged from 2% to 5% (data not shown in Table 1).

A more recent retrospective analysis from the M.D. Anderson Cancer Center (data not shown in Table 1) on 126 patients with IBTR as the first failure after breast-conserving surgery defined true local recurrences as those with the same histology located within 3 cm of the primary tumor bed (Huang et al. 2002). Recurrences located further from the primary tumor bed were considered new primary tumors. The mean time to IBTR was 5.6 years for true recurrences and 7.3 years for new primaries. These results support the need for 7 to 8 years of follow-up to compare alternative radiotherapy strategies to reduce the risk of IBTR after breast-conserving surgery.

Another study (not shown in Table 1) compared the effect of 3 different fractionation regimens using whole-breast irradiation: 50 Gy given in 25 fractions, 39 Gy given in 15 fractions, and 42.9 Gy given in 15 fractions (Owen et al. 2006). Although the stated selection criteria were stage 1–3 invasive breast cancer with a maximum of one positive node and no metastases, a companion article on the same study reported that 8.6% of the 1,410 subjects had 4 or more pathologically involved nodes, and 40.6% had no axillary surgery (cN0 and over 50 years). So the patient population is not identical to that usually included in APBI studies. Nevertheless, it is interesting to note

that among those patients alive and not lost to follow-up after 10 years, there was a significant difference in ipsilateral recurrence rates among women who received 42.9 Gy in 15 doses (9.6%; 95% CI: 6.7–12.6) versus those who were given 39 Gy in 15 doses (14.8%; 95% CI: 11.2–18.3;  $\chi^2$  test  $p=0.027$ ). The recurrence rate for the more commonly used regimen of 50 Gy in 25 fractions was 12.1% (95% CI: 8.8–15.5), but it was not statistically different from the other two regimens. Also, of particular important in this report, “the recurrence-free survival curves for the fractionation schedules diverge only after 5 years of follow-up.” One-third of recurrences occurred after 5 years of follow-up; the median follow-up was 9.7 years (interquartile range, 7.8–11.8).

Some proponents of APBI have argued that whole-breast radiation has no effect on recurrences after 5 years and, therefore, 5 years’ follow-up on APBI should be sufficient. According to Benitez et al. (2006), the trials of lumpectomy with and without radiation showed that the incidence of failures in the ipsilateral breast away from the tumor bed is the same whether or not the patient had radiation, i.e., WB-EBRT has no effect on this type of recurrence. Ott et al. (2007) argue as follows: “[T]he slope of the incidence of local recurrences is almost equal for the patients with and without adjuvant whole breast irradiation after breast conserving surgery.... This indicates that the efficacy of a specific radiotherapy treatment could be assessed after just 5 years of follow-up, which support quality-assured multi-catheter brachytherapy APBI.” To support these arguments, the authors cite studies by Clark et al. (1996), Fisher et al. (2002b), and Veronesi et al. (1993). The article by Veronesi et al. cannot shed light on this issue, since the median follow-up reported in this article was only 39 months. The Clark et al. study also includes a broader range of patients, e.g., patients with larger tumors, who are likely to have higher recurrence rates a priori.

The Fisher et al. and Clark et al. articles do not formally compare the incidence of recurrences between the two study arms, let alone recurrences elsewhere in the ipsilateral breast. Visual inspection of the graphs showing recurrences over time is not sufficient to determine whether or not the incidence of recurrences after 5 years is equivalent or close to equivalent in the groups treated with and without radiation. This is particularly true since the popula-

tion at risk declines substantially the longer the follow-up, which means that the uncertainty around the estimated curve is greater the longer the follow-up. Furthermore, the curves are smoothed in the graphical presentation in some of the articles, which makes a visual inspection even more problematic.

A quantitative analysis is needed to determine whether or not the incidence of recurrences in patients undergoing radiation therapy is the same as for those with no radiation therapy after 5 years of follow-up. All studies on this issue should be considered, including for example, the Early Breast Cancer Trialists' Collaborative Group meta-analysis (EBCTCG 2005). To use the results of such analyses in determining the appropriate follow-up period for APBI, the patient populations must also be similar to those in the APBI trials. If and when such an analysis confirms that WB-EBRT has no impact on recurrences after 5 years in a similar patient population, the length of follow-up period needed to demonstrate the efficacy of APBI can be reconsidered. In the meantime, however, and given the above evidence, follow-up of 7 to 8 years is needed to demonstrate whether APBI is equivalent to WB-EBRT in preventing recurrences. Even longer may be needed to demonstrate the impact on mortality, as the Early Breast Cancer Trialists' Collaborative Group (EBCTCG 2005) has demonstrated, not surprisingly, that the impact on mortality takes longer to manifest.

#### **Accelerated Partial-Breast Irradiation Techniques**

Various techniques are used for breast brachytherapy (Nag 1995; Pieters et al. 1995; Kuske 1999; Nag et al. 2001; Vicini et al. 2002). They differ in the sequence for placing implants and other components of BCT, dose rate and loading technique, and the radioisotopes used. Most older studies of local boost irradiation in BCT implanted the needles, wires, or seeds for brachytherapy after recovery from surgical tumor excision and WB-EBRT. More recently, investigators have perioperatively implanted the hollow needles and catheters that guide placement of the radioactive material. This can be done during the initial lumpectomy if the decision to use brachytherapy has already been made, or at the time of re-excision if pathologic evaluation of margins shows that additional surgery is necessary. Intraoperative implantation avoids the need for a separate surgical procedure with anesthesia for brachytherapy.

Several other brachytherapy devices have recently received 510(k) marketing clearance, as well.

Early work with brachytherapy required the implants to be placed by hand. This limited the dose rate that could be used while maintaining the safety of health care personnel. Later, remote afterloading devices became available and allowed use of high dose rate brachytherapy. This shortened treatment times for boost irradiation, and also led to studies of APBI using brachytherapy as the only form of irradiation in BCT.

The earliest studies of brachytherapy for breast cancer implanted radium needles. Most modern studies on brachytherapy for stage I or II breast cancer used iridium-192 in the form of wires or needles (Nag 1995; Kuske 1999; Nag et al. 2001; Vicini et al. 2002). Some used seeds containing iodine-125 in place of iridium-192. Theoretical advantages of the lower energy emission of iodine-125 include improved shielding to protect health care personnel and visitors, and better spacing of the seeds to improve dose homogeneity within the treatment volume. However, data are unavailable from randomized trials to compare outcomes of different radioactive sources for brachytherapy.

In 2002, a new brachytherapy device was approved by the U.S. Food and Drug Administration (FDA)—the MammoSite™ radiation therapy system, originally from Proxima Therapeutics and now from CYTYC. It consists of a dual lumen catheter with a silicone balloon and an applicator shaft that permits access through an external port (Edmundson et al. 2002). The device is implanted in the lumpectomy cavity during or shortly after breast-conserving surgery. The balloon is inflated with sterile solution of contrast media in saline, and its position is confirmed radiographically using computed tomography. A high dose rate source of iridium-192 is then centrally positioned within the applicator by a remote afterloader. This system is used to deliver 34 Gy in 10 fractions over 5 days.

External-beam radiation treatment modalities developed in other contexts are now being applied to APBI as well. They include 3D-CRT and IMRT. In addition, intraoperative techniques have been developed, including ELIOT (intraoperative therapy with electrons; Veronesi

et al. 2005). With ELIOT, patients receive about 21 Gy intraoperatively, which is reported to be biologically equivalent to 58 to 60 Gy in standard fractionation. A first report on using permanent  $^{105}\text{Pd}$  seed implants, similar to the technique used in early stage prostate cancer, has recently been published as well (Pignol et al. 2006).

**FDA Status.** Iodine-125 seeds were marketed prior to the enactment of the 1976 Medical Device Amendments. Thus, they were cleared for marketing on a “grandfathered” basis. Subsequent radioactive isotope implants, including iridium-192, were approved via 510(k) as substantially equivalent to the radioactive iodine seeds.

A number of breast brachytherapy devices have received U.S. Food and Drug Administration (FDA) 510(k) marketing clearance. The MammoSite™ RTS was cleared for marketing via 510(k) in May 2002 as substantially equivalent to other commercially available brachytherapy applicators used with sealed radiation sources. The FDA’s Office of Device Evaluation judged it reasonably likely that the device will be used in ways outside those specified in the proposed labeling, and that such use could cause harm. Therefore, the FDA required inclusion of the following statement in the “Warnings” section of the device’s labeling: “The safety and effectiveness of the MammoSite RTS as a replacement for whole breast irradiation in the treatment of breast cancer has not been established.”

In December 2005, the FDA cleared for marketing the Axxent™ Electronic Radiotherapy device (Xoft, Inc., Fremont, CA) via 510(k) as substantially equivalent to the MammoSite™ and other brachytherapy systems. The Axxent™ device is a balloon brachytherapy system that uses a disposable, microminiature radiation source to deliver the radiation rather than radioisotopes.

Three additional devices used for breast brachytherapy recently received 501(k) clearance from the FDA. First is a remote controlled radionuclide applicator system by BioLucent, Inc. (Aliso Viejo, CA), also called the Strut-Adjusted Volume Implant or SAVI™, which was cleared on October 20, 2006. This device is described by the manufacturer as a hybrid approach combining interstitial brachytherapy and balloon brachytherapy. Like balloon brachytherapy, the device is inserted in the

tumor cavity through a small incision. A bundle of catheters is then spread out to form an ellipsoid shape inside the cavity. Second is the Adjustable Multi-Catheter Source Applicator or ClearPath™ from North American Scientific, Inc. (Chatsworth, CA), which was cleared on November 9, 2006. The third is the SenoRad Multi-Lumen Balloon Source Applicator for Brachytherapy from SenoRx, Inc. (Aliso Viejo, CA), which was cleared on May 18, 2007.

## Methods

### Search Methods

A MEDLINE® search was conducted via PubMed, covering references entered into the database between 2004 and December 2006. Key search terms included the Medical Subject Headings (MeSH®) terms “breast neoplasms” and “brachytherapy,” plus text word searching for “breast” and [“brachytherapy” or “radiation” or “radiotherapy”]. The search was limited to articles in English that discussed treatment of human patients. To identify more recent studies, the MEDLINE® search was supplemented by examining reference lists of studies identified in the searches. The search was updated in May 2007, using the search terms “accelerated partial breast irradiation” or “APBI,” “breast neoplasm,” “radiotherapy,” and “brachytherapy.” At that time, 199 citations were reviewed.

### Study Selection

Studies on initial treatment of stage I or II breast cancer were included in this Assessment if they reported outcomes for 25 or more patients treated with APBI after breast-conserving surgery. All controlled studies were included, as were uncontrolled studies with a mean or median follow-up of at least 5 years. Abstracts were excluded.

### Medical Advisory Panel Review

This Assessment was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on February 21, 2007. To maintain the timeliness of the Assessment’s scientific information, literature search updates were performed subsequent to the Panel’s review (see “Search Methods”). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the tables and text where appropriate.

## Formulation of the Assessment

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### Patient Indications

Relevant patients are those who select BCT and radiation therapy for initial treatment of stage I or II breast cancer. Although the precise criteria vary from study to study, in general the focus is on older patients with smaller tumors who are node negative (or have only 1 to 3 positive nodes) with no sign of malignancy in the surgical margins; lobular carcinoma is usually excluded.

A dilemma faced in formulating this Assessment is that breast-conserving surgery followed by postoperative radiotherapy is defined as the standard of care for BCT in current clinical guidelines. However, as discussed in the Background section, 15% to 45% of women who choose breast-conserving surgery refuse postoperative radiotherapy. This decision is counter to the best available evidence from randomized, controlled trials and current clinical guidelines, and usually is made against medical advice. Therefore, the Assessment does not consider this group of patients as a separate indication for brachytherapy. For the same reason, the Assessment does not consider breast-conserving surgery alone without radiotherapy as an alternative to breast-conserving surgery plus APBI using brachytherapy.

### Technologies to be Compared

**Whole-breast external-beam radiotherapy following breast-conserving surgery:** It can be delivered in the form of photons (megavoltage X-rays or  $\gamma$  rays from a cobalt-60 source) or high-energy electrons (6–15 MeV) from a linear accelerator. It is usually given in fractions of 1.5–2.5 Gy per day, 5 days weekly, with a total WB-EBRT dose of 45–50 Gy and a boost dose of 10–20 Gy when included.

**Accelerated partial-breast irradiation following breast-conserving surgery:** This includes interstitial brachytherapy, balloon brachytherapy, intraoperative radiotherapy, 3D-CRT, and IMRT. All of these target the tumor bed and one to several centimeters around it, and they usually take 1 to 5 days. The dose varies by modality.

### Health Outcomes

**Benefits.** The potential health benefits of APBI compared to WB-EBRT include reduced radiation exposure for tissues in the ipsilateral breast outside of the tumor bed, as well as

possibly to adjacent organs, and a shorter treatment period, which may improve the patients' quality of life. APBI might also reduce the complications and improve cosmesis compared to WB-EBRT.

**Harms.** The potential harms associated with APBI include increased recurrences, especially in the ipsilateral breast away from the tumor bed, and a potential increase in mortality compared to WB-EBRT. Recurrence, in turn, may lead to mastectomy, an outcome that the patient sought to avoid in the first place. The different APBI modalities might also have greater or lesser impact on complications and cosmesis. For balloon brachytherapy specifically, there is also a risk of having to have the device explanted and then either have another one implanted or switch to a different modality. For interstitial brachytherapy, a high skill level is required from the treating physician.

### Specific Assessment Question

For women with breast cancer tumors smaller than 2–3 cm, clean margins, and no more than 3 positive nodes, does APBI as sole radiation post breast conserving surgery improve net health outcomes at least as much as WB-EBRT?

## Review of Evidence

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The literature search identified 6 controlled studies (Tables 2 and 3) and 2 uncontrolled studies of APBI after breast-conserving surgery for early stage breast cancer with follow-up of at least 5 years (Tables 4 and 5). For each group, key study features and patient characteristics are summarized in one table (Tables 2 and 4) and outcomes are tabulated in a second (Tables 3 and 5). Twenty-three studies were excluded because the mean or median follow-up period was less than 5 years for an uncontrolled study; the sample size was less than 25; or the study focused solely on complications and cosmesis and did not discuss recurrence and mortality rates. A list of the excluded studies is found in the Appendix.

In general, patients selected for APBI had small, usually unifocal tumors; with margins shown to be free of malignant cells; and minimal tumor dissemination to lymph nodes (Tables 2 and 4). However, the studies varied in quantitative aspects of patient selection criteria such as maximal tumor dimension ( $\leq 2$ , 3, or 4 cm), width of tumor-free margins

**Table 2.** Key Features, Controlled Studies on APBI

Citation, Study Design	Surgical Methods	Radiation Therapy Methods	Other Treatments	Patient Characteristics	Characteristics Used for Matching
Vicini et al. 2003, 2001, 1999a, 1999b, 1998, 1997b; Kini et al. 1998  single center; retrospective matched-pair analysis	gross total resection; re-excision if margin $\leq$ 2 mm; levels I & II axillary dissection	<b>brachyTx:</b> 50 Gy LDR (n=120) or 32-34 Gy HDR (n=79)  <b>WB-EBRT:</b> 45-50 Gy over 5 weeks + boost to $\geq$ 60 Gy	adjuvant tamoxifen, 57%; adjuvant chemoTx, 13%  adjuvant tamoxifen, 57%; adjuvant chemoTx, 4%	med. 65 yrs; 1.2 cm median diam., 12% node+; 86% ER+; 46% PR+  med 64 yrs; 1.3 cm median diam; 12% node+; 86% ER+; 57% PR+	age, tumor size, nodal status, ER status, and adjuvant tamoxifen
Polgar et al. 2002  prospective randomized trial	wide excision; >1 cm margins; axillary dissection to levels $\geq$ II	<b>tumor bed only:</b> 36.4 Gy HDR, n=46 (73%); or 50 Gy wide-field local EBRT, n=17 (27%)  <b>WB-EBRT:</b> 50 Gy, 2 Gy fractions; no boost	69 (55%) given adj. hormonal Tx or chemoTx; no information by study arm	mean 59 yrs; 25% premenopausal; 1.4 cm med. diam.; 5% node+; 90% ER+  mean 58 yrs; 24% premenopausal; 1.4 cm median diam.; 3% node+; 84% ER+	not applicable
Polgar et al. 2004  single center; concurrent controls	wide excision; boundaries marked with clips; axillary dissection (77.8% of brachyTx gp; 97.5% of controls); sentinel node biopsy (4.4% of brachyTx gp)	<b>Interstitial HDR brachytherapy:</b> 30.3 Gy HDR (n=8) or 36.4 Gy HDR (n=37)  <b>WB-EBRT:</b> 50 Gy (n=80); 10-16 Gy boost (n=36)	chemoTx or hormonal Tx: 16% each of intervention gp and controls	mean 56 yrs; 36% premenopausal; 80% pN0 and 18% N0; 82% ER+  mean 58 yrs; 28% premenopausal; 95% pN0 and 2.5% N0; 72% ER+	none; controls had to meet same eligibility criteria as intervention group
King et al. 2000  single center; concurrent controls	segmental excision; negative inked margins; level I & II axillary dissection	<b>brachyTx:</b> 32 Gy HDR, n=26; 45 Gy LDR, n=25  <b>WB-EBRT:</b> n=94; mean 59 Gy	n=22 (43%) adj. tamoxifen; n=11 (22%) adj. chemoTx  n=46 (49%) adj. tamoxifen; n=25 (17%) adj. chemoTx	mean 63 yrs; 12% premenopausal; 1.4 cm mean diam.; 18% node+; ER status NR  mean 57 yrs; 27% premenopausal; 1.5 cm mean diam.; 15% node+; ER status NR	pathologic stage, tumor size, breast size

**Table 2.** Key Features, Controlled Studies on APBI (cont'd)

Citation, Study Design	Surgical Methods	Radiation Therapy Methods	Other Treatments	Patient Characteristics	Characteristics Used for Matching
Fentiman et al. 1996, 1991  nonrandomized, retrospective, unmatched controls	excision biopsy or gross excision; axillary clearance	<b>brachyTx:</b> n=27, 55 Gy HDR  <b>WB-EBRT:</b> n= 221, 46 Gy + 20 Gy boost	adjuvant Tx only if node+: tamoxifen if postmenopausal, CMF chemoTx if premenopausal	mean 51 yrs; 33% premenopausal, 3.0 cm mean diam.; 44% node+; 56% margin+  data NR for controls	none specified
Ott et al. 2005  nonrandomized, retrospective, unmatched controls	BCS	<b>Interstitial APBI:</b> 49.8 Gy PDR, n=27; 32 Gy HDR, n=6  <b>EBRT ± boost:</b> 50.4 Gy + boost with median 12 Gy  <b>EBRT + brachyTx:</b> 50.4 Gy + median 12.3 Gy PDR, n=12, or median 10 Gy HDR, n=10	n=21 antihormonal; n=2 chemoTx and antihormonal  n=12 antihormonal; n=4 chemoTx; n=5 both  n=6 antihormonal; n=6 chemoTx; n=9 both	median age 51–59	comparable follow-up period and complete series of mammograms during follow-up

**Abbreviations**

adj	adjuvant
APBI	accelerated partial-breast irradiation
BCS	breast-conserving surgery
brachyTx	brachytherapy
chemoTx	chemotherapy
CMF	cyclophosphamide, methotrexate, 5-fluorouracil
diam	diameter
ER	estrogen receptor
gp	group
Gy	gray;
HDR	high dose rate
LDR	low dose rate
NR	not reported
PDR	pulsed dose rate
PR	progesterone receptor
tx	therapy
WB-EBRT	whole-breast external-beam radiotherapy

**Table 3.** Outcomes from Controlled Studies on APBI using Brachytherapy in Patients Undergoing BCT for Breast Cancer

Citation	Type of Radiotherapy	n	Median Follow-up (months)	Primary Site Failure (%)	Other Ipsilateral Failure (%)	Regional (Nodal) Failure (%)	Contralateral Failure (%)	Median Time to Failure (months)	Distant Metastasis (%)	Cosmetic Outcomes	Adverse Effects
Vicini et al. 2001, 2003  (includes 41 patients who did not meet the eligibility criteria)	brachyTx	199	60	0.5 (at 5 years)	0.6 (at 5 years)	1 (at 5 years)	1 (at 5 years)	not reported*	3 (at 5 years)	n=89; 90% good or excellent; 1% poor	3% pain; 4% fat necrosis
	whole-breast EBRT	199	107	0.5	0.5	1	4		5	n=164; 83% good or excellent; none poor	9% pain; 8% fat necrosis
Polgar et al. 2002	tumor-bed only	63	30	0	0	0	not reported	not reached	5		2% gr. 2 skin rxn.; 10% gr. 2/3 fibrosis; 16% fat necrosis;
	whole-breast EBRT	63		0	0	0			2	not reported	4% gr. 2 skin rxn.; 13% gr. 2/3 fibrosis; 9% fat necrosis;
Polgar et al. 2004	interstitial brachyTx	45	81	0	7	not reported	0	not reported	not reported	84.4% excellent/good; 15.6% fair/poor	4.4% grade 2-3 telangiectasia; 20% grade 2-3 fibrosis; 22.2% fat necrosis (1/9 symptomatic)
	whole breast EBRT	80	83	4	6		4			68.2% excellent/good; 31.7% fair/poor  p=0.04	15.9% grade 2-3 telangiectasia; 12.7% grade 2-3 fibrosis; 20.6% fat necrosis (none symptomatic)
King et al. 2000	brachyTx	51	75	2	0	6	not reported	not reached	8	75% excellent or good; 0% poor	grade III, 8%; grade I/II, 22%
	whole-breast EBRT	94	74	2	3	0			4	84% excellent or good; 1% poor	grade III, 5%; grade I/II, 80%

**Table 3.** Outcomes from Controlled Studies on APBI using Brachytherapy in Patients Undergoing BCT for Breast Cancer (cont'd)

Citation	Type of Radiotherapy	n	Median Follow-up (months)	Primary Site Failure (%)	Other Ipsilateral Failure (%)	Regional (Nodal) Failure (%)	Contralateral Failure (%)	Median Time to Failure (months)	Distant Metastasis (%)	Cosmetic Outcomes	Adverse Effects
Fentiman et al. 1996, 1991	brachyTx	27	72	37		not reported	not reported	not reached	not reported	83% excellent or good, 0% poor	15% wound infection; 26% erythema; 11% skin necrosis
	whole-breast	221	>96	~ 15						not reported	not reported
Ott et al. 2005	A. APBI**	33	35	not reported		not reported	not reported	not reported	not reported		mammographically evident fat necrosis: 15.2 % group A, 20.0% group B, 9% group C (p=NS); clinically evident breast fibrosis LENT-SOMA grade 2: 6.1% in group A, 23.3% in group B, 27.3% in group C (p=0.0004); subjective breast pain LENT-SOMA grade 0: 90.9% for group A, 66.7% for group B, 81.8% for group C (p=0.0498)
	B. Whole-breast + EBRT boost	30	36								
	C. Whole breast w/ interstitial brachyTx boost	22	38							not reported	

\*Median time to local recurrence was 5.0 years in whole breast irradiation group; 5.7 years in brachytherapy group (p=0.82). The specific brachytherapy methods are not described.

\*\* Patients from trial described in Ott et al. 2004, 2007, in Tables 4 and 5.

#### Abbreviations

APBI	accelerated partial-breast irradiation
brachyTx	brachytherapy
chemotx	chemotherapy
EBRT	external-beam radiotherapy
ER	estrogen receptor
HDR	high dose rate
LENT-SOMA	Late Effects on Normal Tissues - Subjective, Objective, Management and Analytic
NS	not significant
rxn	reaction
tx	therapy

**Table 4.** Key Features of Uncontrolled Studies on APBI

Citation	Surgical Methods	APBI Methods	Other Treatments	Patient Characteristics
Polgar et al. 2002, 1999	wide excision, ≥1 cm margin; level ≥II axillary dissection	36.4 Gy HDR, n=46	13% adjuvant hormonal Tx or chemoTx; details NR	mean 56 yrs; 36% premenopausal; 1.2 cm median diam; 2% node+; 82% ER+
Perera et al. 1995, 1997, 2001 (abstract), 2003	lumpectomy or wider excision; axillary dissection, levels unspecified (median no. removed=13)	interstitial: 37.2 Gy HDR brachyTx	tamoxifen if node+, ER+ & post-menopause, or if node- ER+ & large tumor; adj. chemoTx if node+ ER- or if node-, ≤65 & poorly differentiated, larger tumors	median 59 yrs; 1.6 cm mean diam; 15% node+; n=13, tamoxifen, n=4 chemoTx

**Abbreviations**

APBI: accelerated partial-breast irradiation; brachyTx: brachytherapy; chemotx: chemotherapy; diam: diameter; ER: estrogen receptor; HDR: high dose rate; NR: not reported; tx: therapy

**Table 5.** Outcomes from Uncontrolled Studies on APBI using Brachytherapy in Patients Undergoing BCT for Breast Cancer

Citation	n	Median Follow-up (months)	Primary Site Failure (%)	Other Ipsilateral Failure (%)	Regional (Nodal) Failure (%)	Contralateral Failure (%)	Median Time to Failure (months)	Distant Metastasis (%)	Cosmetic Outcomes	Adverse Effects
Polgar et al. 1999, 2002	45	57	0	4	4	0	not reached	6	excellent, 98%	1 each, arterial bleed & hematoma; 7% gr. 2 skin rxn; 16% gr. 2/3 fibrosis; 4% fat necrosis
Perera et al. 1995, 1997, 2001 (abstract), 2003	39	91	5	10	13	5	not reached	8	average score: 90 (out of 100; range 0-100) at 12 months; scored by patients	6 (15%) gr. 2/3 skin rxn; 7 (18%) moderate discomfort; 5 (13%) fat necrosis

**Abbreviations;** APBI: accelerated partial-breast irradiation; BCT: breast-conserving therapy; rxn: reaction

( $\geq 2$  or 1 mm or not specified), nodal status (node negative or up to 3 positive nodes), and others. Present data are insufficient to define reliably those who are best candidates, or those who should not be considered, for APBI using brachytherapy.

Only one controlled study is a prospective, randomized trial (Polgar et al. 2002). Seventy-three percent of patients (n=46) in the experimental arm were treated with APBI using brachytherapy after breast-conserving surgery (Table 2); the other 27% (n=17) received APBI using wide-field local EBRT. Controls (n=63) received WB-EBRT without local boost. Median follow-up was only 30 months for the 126 patients enrolled by the time of this preliminary report. This is inadequate to permit conclusions for comparing frequencies of ipsilateral breast tumor recurrence (IBTR). Thus far, no patients in either arm experienced IBTR at the excision site or elsewhere in the breast (Table 3). Cosmetic outcomes were not reported. Fat necrosis was reported less frequently in the group treated with WB-EBRT, while skin reactions and fibrosis were reported less often among those treated with brachytherapy.

Another controlled study used a retrospective matched-pair (case-control) design to compare outcomes of APBI using brachytherapy with outcomes of WB-EBRT plus local boost in carefully selected patients who had tumor-free margins  $\geq 2$  mm (Vicini et al. 2001, 2003). Additional eligibility criteria for brachytherapy (n=199) included age older than 40 years, infiltrating ductal histology, absence of an extensive intraductal component, tumor size  $\leq 3$  cm in largest dimension, and  $\leq 3$  lymph nodes positive for malignancy after lymph node dissection to levels I and II of the axilla. Patients with lobular carcinoma, ductal carcinoma in situ, or skin involvement were excluded from APBI using brachytherapy. Identical criteria were used to select controls (n=447) from all patients given WB-EBRT after breast-conserving surgery over 16 years. Controls were then matched to brachytherapy cases for age ( $\pm 10$  years), tumor size ( $\pm 5$  mm), nodal status, estrogen receptor status, and use of adjuvant tamoxifen. For each brachytherapy patient, one control patient was randomly selected (with outcomes blinded) from those well-matched for specified characteristics. Multiple earlier reports included many of the brachytherapy patients from this retrospective series, but without controls (Vicini et al. 1997b, 1998, 1999a, 1999b; Kini et al. 1998).

In the Vicini study (2001), median follow-up for the 199 brachytherapy patients was 60 months, but it was 107 months for the 199 matched controls (Table 3). Actuarial analysis was used to estimate rates of IBTR at 5 years after treatment, which was reportedly 0.5% for both the brachytherapy patients and the WB-EBRT controls.

Several other problems with this analysis should be mentioned. The published report did not show Kaplan-Meier curves from actuarial analyses for survival or other outcomes. Follow-up was insufficient to estimate recurrence rates after 5 years. Additionally, significantly more patients given partial-breast irradiation received adjuvant chemotherapy, were re-excised to achieve tumor-free margins  $\geq 2$  mm on all sides, and significantly fewer had contralateral breast cancer at 5 years (suggesting different recurrence risks despite matching). These differences may have biased the comparison in favor of partial-breast irradiation, and underscore the uncertainties associated with using historical controls to compare partial- and whole-breast radiation after breast-conserving surgery. A more recent report on the 199 patients given APBI included a median 6.4 years follow-up, but only reported cosmetic outcomes and treatment-related toxicities (Chen et al. 2006). Consequently, this study (Vicini et al. 2001, 2003) also is insufficient to permit conclusions for comparing frequencies of IBTR after APBI using brachytherapy or WB-EBRT following breast-conserving surgery.

Among patients observed for at least 36 months, cosmesis was rated excellent or good in 90% of those treated with APBI using brachytherapy (n=89) and 83% of those (n=137) treated with WB-EBRT (Vicini et al. 2001). Statistically, these results were not significantly different. The decreases reported in frequencies of breast pain (3% versus 9%) and asymptomatic fat necrosis (4% versus 8%) for the group treated with APBI using brachytherapy also were not statistically significant.

A second nonrandomized but controlled study compared interstitial brachytherapy in 45 subjects with WB-EBRT among 90 controls who met the eligibility criteria for the intervention group (Polgar et al. 2004). This study had nearly 7 years of follow-up data, and differences in the actuarial rates of ipsilateral breast recurrence at 5 and 7 years were not statistically significant. However, the trial was

not designed to test noninferiority, and the lack of a significant difference is inconclusive since the sample size was small and few in-breast failures occurred in either arm (3 in the APBI group; 8 in the WB-EBRT group).

A third nonrandomized analysis compared outcomes for 50 patients (51 breast cancers) given breast-conserving surgery plus APBI using brachytherapy with outcomes for 94 patients who met eligibility criteria for APBI using brachytherapy, but were treated concurrently with WB-EBRT (King et al. 2000). The analysis for IBTR frequency compared patients given APBI using brachytherapy with all WB-EBRT patients, without matching for prognostic factors known to affect the likelihood of relapse (Table 2). In contrast, the comparison of cosmetic outcomes used a subset of WB-EBRT control patients matched to patients given APBI using brachytherapy for pathologic stage, tumor size, and breast size.

At a median follow-up of 74 to 75 months, few ipsilateral recurrences were observed in either group (Table 3). For those given APBI using brachytherapy, 2% had IBTR at the excision site and 6% had nodal failure. For those given WB-EBRT, 2% had IBTR at the excision site, 3% had IBTR elsewhere in the breast, and none had nodal failure. The study reported no statistically significant differences between groups in cosmetic results or in grade III toxicities that required surgical intervention. However, grade I and II complications were significantly more common among those treated with WB-EBRT (22% versus 80%,  $p < 0.001$ ).

The King study (2000) differed from others by including patients with larger tumors (up to 4 cm), those with carcinoma in situ (10% of patients given APBI using brachytherapy and 36% of WB-EBRT controls), and those with extensive intraductal carcinoma (14% to 15% of each group). Information on some aspects of WB-EBRT (fractionation, local boost) was inadequate. Of greatest concern, no information was provided on factors patients and physicians used to select treatment with APBI using brachytherapy or WB-EBRT. Consequently, patient selection bias confounds these results and the study does not permit conclusions.

The earliest controlled study (Fentiman et al. 1996, 1991) likely is not applicable to patients currently considered eligible for APBI using brachytherapy after breast-conserving surgery

(Table 2). More than half the patients had positive margins after excision and were not subjected to re-excision. Three of 27 (11%) did not meet the study's eligibility criteria since their tumors were larger than 4 cm in largest dimension. There was no upper limit on the number of positive lymph nodes, 44% of patients had nodal involvement, and neither the number of involved nodes per patient nor the frequency of greater than 3 positive nodes was reported. Of even greater concern, no data were provided on patient or tumor characteristics of controls, and no effort was made to select matched controls. Finally, APBI using brachytherapy as delivered in this study did not include current methods of dosimetry and quality control.

As shown in Table 3, Fentiman et al. (1996) reported that IBTR was more frequent among patients given APBI using brachytherapy (37% of 27 patients at 72 months median follow-up) than among WB-EBRT controls (15% of 221 patients at greater than 96 months' follow-up). Nevertheless, these results do not permit conclusions since data were insufficient to evaluate the comparability of treatment groups. Note also that data on cosmetic outcomes (85% excellent or good) and adverse effects were included only for those given brachytherapy.

The final controlled study (Ott et al. 2005) compared 33 patients undergoing APBI, 30 patients having WB-EBRT with or without a boost to the tumor bed, and 22 patients undergoing WB-EBRT with an interstitial brachytherapy boost. The median follow-up for the 3 groups ranged from 35 to 38 months. However, this article did not report any information on recurrences or mortality; it focused solely on complications. It reported that there was no significant difference in the rates of fat necrosis across the three groups. Clinically evident breast fibrosis was significantly less likely in the APBI group (6% vs. 23–27% in the WB-EBRT groups), and subjective breast pain was more common in the APBI group (90.9% vs. 66.7% for group with WB-EBRT  $\pm$  EBRT boost and 81.8% in group with WB-EBRT and interstitial boost;  $p = 0.0498$ ).

Tables 4 and 5 summarize evidence from two uncontrolled studies with a total of 84 patients. The Polgar et al. study (1999, 2002) was included, even though the median follow-up is 3 months short of the designated 5-year follow-up. Table 5 shows that one of the studies reported recurrence at the excision site and 4–10% of patients experienced other ipsilateral

failures. The Perera et al. studies (1995, 1997, 2001, 2003) included node-positive patients, which may help account for the higher rate of nodal failure in this study (13% vs. 5% in Polgar et al. [1999, 2002]). Cosmetic outcomes were good to excellent for most patients, and few major complications were reported. Nevertheless, results from uncontrolled studies may be confounded by patient selection biases. Thus, these two uncontrolled series summarized in Tables 4 and 5 also do not permit conclusions for comparing frequencies of IBTR after APBI using brachytherapy or WB-EBRT for women given breast-conserving surgery.

Current brachytherapy methods use computerized treatment planning to define target volumes and deliver radiotherapy with improved conformality, when compared with conventional EBRT. Some have hypothesized that increasing the conformality of radiotherapy may reduce non-breast cancer (vascular) deaths after BCT that includes postoperative radiation. However, Kaplan-Meier curves did not begin to show separation until more than 5 years after treatment in the meta-analysis that reported increased non-breast deaths among those randomized to postoperative radiation (Early Breast Cancer Trialists' Cooperative Group 2000). Thus, the duration of follow-up in current reports on breast-conserving surgery followed by APBI using brachytherapy also is inadequate to determine whether increased conformality reduces non-breast cancer deaths when compared with breast-conserving surgery plus WB-EBRT.

The American Society of Breast Surgeons MammoSite Breast Brachytherapy Registry Trial included 1,419 patients with Stage 0, I, or II breast carcinoma undergoing breast-conserving therapy (Vicini et al. 2005). The device was placed in 1,403 patients, and 1,237 patients received APBI (in an additional 43, balloon brachytherapy was used to deliver a boost). Sixteen patients did not have devices implanted because of positive lymph nodes (n=9), patient request (n=4), or lobular histology (n=3). One hundred and twenty-three patients, or 10% of those with the devices implanted, had their devices explanted: 43 (35%) were due to inadequate skin distance, 35 (28.5%) due to poor cavity conformance, 13 (10.6%) due to positive margins, 11 (8.9%) due to balloon failure, 9 (7.3%) due to positive lymph nodes, and 12 (9.8%) for other reasons.

In an editorial Prosnitz and Marks (2006) argue that APBI might be considered the "radiotherapeutic equivalent of a surgical quadrantectomy." They then summarize the results of a trial in Milan comparing surgical quadrantectomy with and without whole-breast irradiation (Veronesi et al. 2001a). With about 600 patients, the trial found that the recurrence rate at 10 years was about 6% for those receiving radiation versus 24% for those that did not. In subgroup analyses, the only group that radiation treatment did not seem to benefit was patients 65 years or older. They also note that some of the initially favorable trials of APBI have relatively older patient populations.

Although all forms of APBI use radiation to treat the tumor bed and a centimeter or two around it, the specific techniques vary. Brachytherapy and intraoperative radiotherapy irradiate the area from the inside, while 3D-CRT, IMRT, and other types of external beam radiation irradiate the area from the outside. The techniques used to identify the tumor volume and to develop the radiation plan vary both within and across techniques. The specific doses provided per treatment and the spacing of the treatments also varies: for example, intraoperative radiotherapy consists of a single dose during the surgery, while receiving 10 doses over 5 days beginning days or weeks after surgery is a common protocol other types of APBI.

There are some dosimetric studies comparing two or more of these modalities, but they are usually based on treatment plans for a limited number of subjects. For example, Major et al. (2006) conducted a quantitative dosimetric comparison of interstitial and balloon brachytherapy and found that dose homogeneity was better for balloon brachytherapy but the dose to the skin and lung was higher. In another study comparing balloon brachytherapy, IMRT, and 3D-CRT (Khan et al. 2006), the mean ipsilateral breast dose  $V_{50}$  (i.e., percentage of breast receiving 50% of the prescribed dose) was 29% for balloon brachytherapy, 56% for 3D-CRT, and 46% for IMRT ( $p < 0.0001$ ). However, the corresponding mean heart  $V_5$  (i.e., percentage of heart receiving 5% of the prescribed dose) values were 12%, 4%, and 1% ( $p < 0.01$ ). Based on a search of the more recent literature, we did not find any studies that calculated actual doses using phantoms.

Given the variation across these techniques—for example, with skin doses likely to be higher with external beam radiation and dose homogeneity potentially a greater issue with brachytherapy—long-term follow-up is needed to determine the effects of each modality compared to whole-breast irradiation. The evidence is not sufficient to support the assumption that findings for one type of APBI—for example, interstitial brachytherapy—can be extrapolated to other types of brachytherapy.

There are a number of randomized, controlled trials on the use of APBI currently underway, comparing whole-breast irradiation to 1) intraoperative electron beam radiation therapy (European Institute of Oncology, n=824); 2) interstitial or balloon brachytherapy or 3D-CRT (NSABP B 39/RTOG 0413, n=3,000); 3) interstitial brachytherapy (European Brachytherapy Breast Cancer GEC-ESTRO, n=1,170); 4) interstitial brachytherapy or electrons (National Institute of Oncology, Hungary, n=570); and 5) 3D-CRT (Ontario Clinical Oncology Group, n=2,128) ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) and Marsiglia and Chajon 2006).

## Discussion and Conclusions

To assess APBI as a sole alternative to WB-EBRT, trials are needed that compare the two approaches in similar populations (ideally randomized) for at least 8 years. In a patient-level meta-analysis, the Early Breast Cancer Trialists' Collaborative Group found that the use of WB-EBRT reduced 15-year breast cancer absolute mortality risk by 5.4%, from 35.9% to 30.5% (SE=1.7, 2p=0.0002); there was a similar reduction in absolute mortality from all causes of 5.3% (SE=1.8, 2p=0.005). Thus, evidence clearly demonstrates that radiotherapy following BCS reduces recurrences and prolongs survival.

There are 32 studies on APBI, but only 6 are controlled studies; and the rest are uncontrolled. There is only one small, randomized trial (n=126) with inadequate follow-up (30 months). It is uncertain whether controls in the nonrandomized studies are sufficiently similar to the intervention groups. Recurrence rates vary substantially based on multiple clinical factors, not all of which have been identified; thus, one cannot be sure that 5-year recurrence rates in non-randomized trials are equivalent between WB-EBRT treatment and APBI. Given

the various APBI techniques, there may also be differences in dosimetry, delivery, and adverse effects, and outcomes among the modalities. There is only one small, randomized trial (n=126) with inadequate follow-up (30 months). It is uncertain whether controls in the non-randomized studies are sufficiently similar to the intervention groups. Recurrence rates vary substantially based on multiple clinical factors, not all of which have been identified; thus, one cannot be sure that recurrence rates in the first 5 years are equivalent between whole-breast radiation treatment and APBI. Given the various APBI techniques, there may also be differences in dosimetry, delivery, recurrence, and adverse effects among the modalities.

Few of the existing studies have adequate follow-up. Studies on the effect of radiation treatment following lumpectomy originally showed that it reduced recurrences but had no impact on mortality. This led some to hypothesize that the beneficial effects of radiation in reducing recurrences were possibly offset by deaths from other causes (e.g., heart and lung disease) due to the radiation exposure of adjacent organs. With longer follow-up, it became clear that radiation therapy reduced mortality as well as recurrences, although perhaps not to the same degree. The question with APBI is whether whole-breast radiation also reduces recurrences after more than 5 years of follow-up and particularly decreases recurrences in the ipsilateral breast away from the tumor bed (an area not treated by APBI).

The apparent lack of a significant short-term difference between APBI and WB-EBRT for interstitial brachytherapy merits further investigation. At present, the sample sizes are quite small in most studies relative to the frequency of the outcome of interest (short-term recurrence and death). Another unknown is the impact of the differences in dosimetry, delivery, etc., across the various APBI modalities. With balloon brachytherapy, around 10% of devices are explanted, because of inadequate distance from the skin, lack of conformance with the lumpectomy cavity, positive margins, balloon failure, or other reasons. A number of randomized trials are now underway that should answer many of the remaining questions regarding APBI. However, it will be a number of years before results are available on 8-year follow-up. At present, evidence is insufficient to determine whether APBI is at least as good

as WB-EBRT in reducing recurrences and mortality.

Some proponents of APBI have pointed to the number of women who forego radiotherapy following BCS. They assert that APBI is more convenient than WB-EBRT, and therefore, its availability might reduce the number of patients with no radiotherapy. Radiotherapy use is less frequent among African-Americans and those living farther from radiotherapy facilities; however, adequate information is lacking on other factors influencing women who do not get radiotherapy. Therefore, it is not known whether patients currently omitting radiotherapy would choose APBI if it were readily available. Also, some women may choose to forego radiotherapy because of age, as suggested in the NCCN guidelines, or the presence of other life-threatening comorbidities.

Furthermore, if convenience is the primary impediment to getting radiotherapy following BCS, several accelerated whole-breast protocols have been tested. For example, a randomized controlled trial in Canada compared the traditional 50-Gy protocol delivered in 25 fractions over 35 days with an accelerated protocol of 42.5 Gy delivered in 16 fractions over 22 days. With 1,234 patients followed a median of 69 months, there was no statistically significant difference in local recurrence-free, disease-free, or overall survival between the two regimens (Whelan et al. 2002). Another study comparing 3 whole-breast fractionation regimens suggested that hypofractionation is a reasonable alternative; a larger trial is underway to confirm these findings (Owen et al. 2006; Yarnold et al. 2005). Other accelerated, whole-breast regimens are currently being tested, but the studies reported to date are uncontrolled and the follow-up is too short to evaluate the impact on recurrence rates (Formenti et al. 2007; Freedman et al. 2007). Because accelerated whole-breast irradiation changes only one parameter in the traditional radiotherapy regimen, i.e., fraction size but not the breast volume treated, it may be a more conservative approach than APBI for women who do not want to undergo the traditional 5- to 6-week protocol. This may be a more prudent approach until further follow-up reveals the long-term efficacy of APBI versus the traditional WB-EBRT protocol.

## Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether accelerated partial-breast irradiation (APBI) as sole radiotherapy meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria to decrease recurrence after breast-conserving surgery for early stage breast cancer.

### 1. The technology must have final approval from the appropriate governmental regulatory bodies.

Iodine-125 seeds were marketed prior to enactment of the 1976 Medical Device Amendments. Thus, they were cleared for marketing on a “grandfathered” basis. Subsequent radioactive isotope implants, including iridium-192, were approved via 510(k) as substantially equivalent to the radioactive iodine seeds.

A number of breast brachytherapy devices have received U.S. Food and Drug Administration’s (FDA) 510(k) marketing clearance. The MammoSite™ RTS was cleared for marketing via 510(k) in May 2002 as substantially equivalent to other commercially available brachytherapy applicators used with sealed radiation sources. The FDA’s Office of Device Evaluation judged it reasonably likely that the device will be used in ways outside those specified in the proposed labeling, and that such use could cause harm. Therefore, the FDA required inclusion of the following statement in the “Warnings” section of the device’s labeling: “The safety and effectiveness of the MammoSite RTS as a replacement for whole breast irradiation in the treatment of breast cancer has not been established.”

In December 2005, the FDA cleared for marketing the Axxent™ Electronic Radiotherapy device (Xoft, Inc., Fremont, CA) via 510(k) as substantially equivalent to the MammoSite™ and other brachytherapy systems. The Axxent™ device is a balloon brachytherapy system that uses a disposable, microminiature radiation source to deliver the radiation rather than radioisotopes.

Three additional devices used for breast brachytherapy recently received 501(k) clear-

ance from the FDA. First is a remote-controlled radionuclide applicator system by BioLucent, Inc. (Aliso Viejo, CA), called the Strut-Adjusted Volume Implant or SAVI™, which was cleared on October 20, 2006. This device is described by the manufacturer as a hybrid approach, combining interstitial brachytherapy and balloon brachytherapy. Like balloon brachytherapy, the device is inserted in the tumor cavity through a small incision. A bundle of catheters is then spread out to form an ellipsoid shape inside the cavity. Second is the Adjustable Multi-Catheter Source Applicator or ClearPath™ from North American Scientific, Inc. (Chatsworth, CA), which was cleared on November 9, 2006. The third is the SenoRad Multi-Lumen Balloon Source Applicator for Brachytherapy from SenoRx, Inc. (Aliso Viejo, CA), which was cleared on May 18, 2007.

**2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.**

The Assessment sought to compare outcomes of APBI, with those of WB-EBRT, after breast-conserving surgery. Follow-up of at least 8 years is needed to demonstrate their equivalence.

The single randomized, controlled trial reported follow-up of only 30 months, far short of the minimum needed. Other studies reported on longer follow-up but were uncontrolled, did not report on recurrences, included patients who did not meet the eligibility criteria, or had other important flaws. All of the studies that met the study selection criteria for this Assessment focused on interstitial brachytherapy, a technique with a steep learning curve for practitioners. These findings cannot be extrapolated automatically to other types of APBI.

Consequently, the evidence on APBI as sole radiotherapy for early stage breast cancer is insufficient to permit conclusions concerning its effect on health outcomes.

**3. The technology must improve the net health outcome.**

Since available evidence is insufficient to permit conclusions, it cannot be determined whether APBI as sole radiotherapy improves net health outcomes of women undergoing breast-conserving surgery for early stage breast cancer.

**4. The technology must be as beneficial as any established alternatives.**

Since available evidence is insufficient to permit conclusions, it cannot be determined whether APBI as sole radiotherapy is as beneficial as WB-EBRT after breast-conserving surgery for early stage breast cancer.

**5. The improvement must be attainable outside the investigational settings.**

Whether APBI using as sole radiotherapy improves health outcomes after breast-conserving surgery for early stage breast cancer has not been demonstrated in the investigational setting.

Based on the above, accelerated partial breast irradiation as the sole radiation treatment after breast-conserving surgery for early stage breast cancer does not meet the TEC criteria.

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# Appendix

## Excluded Articles

### Sample Size Less than 25

Stevens MJ, Cooper SG, Cross P et al. (2006). Accelerated partial breast irradiation using interstitial high dose rate <sup>192</sup>iridium brachytherapy: Early Australian experience and review of the literature. *Australasian Radiol*, 50:143-151.

### Uncontrolled Studies with Follow-up Less than 5 Years

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### Small Sample and Follow-up Less than 5 Years

Niehoff P, Polgar C, Ostertag H et al. (2006). Clinical experience with the MammoSite<sup>®</sup> radiation therapy system for brachytherapy of breast cancer: Results from an international phase II trial. *Radiother Oncol*, 79:316-20.

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